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ORIGINAL ARTICLE

Prognostic factors in a cohort of antisynthetase syndrome (ASS): serologic profile is associated with mortality in patients with interstitial lung disease (ILD)

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Abstract The objectives of the present study were to compare the survival function of antisynthetase syndrome (ASS) Jo1-positive patients with ASS non-Jo1 patients, all with interstitial lung disease (ILD), and to evaluate other factors such as the extension of pulmonary disease and the time between the onset of symptoms and diagnosis and its association to survival in a cohort of ASS patients. Patients with ASS, all with ILD, were included. At the baseline, pulmonary function tests were realized and a high-resolution chest tomography was obtained; lung inflammation and fibrosis were measured with the Goh score and the Kazerooni index. The following autoantibodies were measured: Jo1, Ej, Oj, PL7, and PL12. Patients had to be positive for one of them in order to be included in the study. The survival function was estimated and compared with the log rank test, and the hazard ratio (HR) was estimated using Cox regression procedure. Forty-three patients were included, of which six patients died (14 %). Patients who died were different in comparison with survivors as regards the frequency of anti-Jo1 positivity: Survivors had anti-Jo1 autoantibodies more frequently (86 %) than patients who died (50 %). The univariate Cox regression analysis identified four variables associated with survival: Jo1 status, arthritis, extent of ground glass, and consolidation (inflammation) in high-resolution computed tomography (HRCT) and baseline forced vital capacity. The serological status of patients (Jo1-positive vs non-Jo1), the extent of lung inflammation in the HRCT scan, a low forced vital capacity, and arthritis are associated with survival in ASS patients.

Keywords Antisynthetase antibodies · Antisynthetase syndrome · Interstitial lung disease · Jo1 autoantibody

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Introduction

Antisynthetase syndrome (ASS) is a clinical condition characterized by arthritis, mechanic's hand sign, interstitial lung disease (ILD), fever, Raynaud´s phenomenon, and myositis [1]. ASS is associated with aminoacyl-transfer RNA synthase (ARS) autoantibodies, which include anti-Jo1 (anti-histidyl), anti-EJ (anti-glycyl), anti-OJ (anti-isoleucyl), anti-PL7 (anti-threonyl), anti-PL12 (anti-alanyl), anti-SC (anti-lysil), anti-KS (anti-asparaginyl), anti-JS (anti-glutaminyl), anti-Ha or anti-YRS (anti-threonyl), anti-tryptophanyl, and anti-Zo (anti-phenylalanyl) autoantibodies, with anti-Jo1 being the most common [1, 2]. ILD is by far the most severe manifestation of ASS, occurs in around 80 % of ASS patients, and is associated with high morbidity and mortality. [3, 4] Current treatment is based on corticosteroids and a wide number of immunosuppressive drugs, although no clinical trials on this condition have been reported.

Prognostic factors in ILD related to ASS have not being entirely defined. Marie et al. described the presence of anti-PL7 or PL12 antibody as being associated with early and

severe ILD [5]. Moreover, it has been reported that non-Jo1 patients may have decreased survival compared to Jo1 patients and that ILD is also related to worse prognosis [6, 7]. It is not clear if the inferior survival rate observed in non-jo1 ASS is related to the higher incidence of ILD. With this background, it seems relevant to evaluate if patients with ASS and ILD have different prognosis according to the serological profile and to evaluate if other factors such as the extension of pulmonary disease are associated with survival. In this study, our aims were to compare the survival function of ILD-ASS Jo1-positive patients with ILD-ASS non-Jo1 patients and to evaluate other factors possibly associated with survival such as extension of pulmonary disease and the time between the onset of symptoms and diagnosis of ASS.

Patients and methods

All patients were referred to the interstitial lung disease clinic, at the Instituto Nacional de Enfermedades Respiratorias, Ismael Cosio Villegas, a tertiary care referral center for respiratory diseases, for the evaluation of their respiratory symptoms. We included patients evaluated in the period from March 2006 to December 2014 who were clinically assessed by pulmonologists and a rheumatologist seasoned in the evaluation and management of ILD. Based on this evaluation, autoantibody serological tests were done according to the pre-test probability of diagnosis. Patients were included in this study as ASS if a diagnosis of ILD was confirmed (TLC <80 %, normal FEV1/forced vital capacity (FVC) and FVC <80 %, evidence of ILD in high-resolution computed tomography (HRCT)), as well as at least two of the following criteria: idiopathic inflammatory myopathy (IIM) according to Bohan and Peter´s criteria [8, 9], fever, arthritis, and mechanic's hands sign. Patients had to have at least one of the following autoantibodies: Jo1, Ej, Oj, PL7, or PL12. If a patient did not fulfill the proposed criteria, he or she was classified as having a lung dominant connective tissue disease and was not included in the study [10]. We reviewed their medical records to register baseline pulmonary function tests which included diffusing capacity of the lung for carbon monoxide (DLCO), spirometry, and plethysmography. Their serum creatine kinase level was registered, as well as the history of Raynaud's phenomenon, sclerodactyly, dermatomyositis rash, and proximal dysphagia. We registered the drugs used to treat patients and the clinical evolution of patients, including time until death or follow-up on the last visit time. A detailed description of the time elapsed between the onsets of respiratory and IIM symptoms was obtained by reviewing clinical charts or direct interview with patients. The local institutional review board approved the study protocol. All patients gave written informed consent to participate in the study.

Autoantibodies The IgG ARS autoantibodies (Jo1, PL7, PL12, Ej, Oj) were measured using EUROIMMUN immunoblot strips (EUROLINE: Myositis Profile 3) according to the manufacturer's instructions. Myositis Profile Euroline is a qualitative line immunoassay for the detection of human IgG autoantibodies. This commercial line blot assay for myositis diagnosis was assessed on its diagnostic accuracy against RNA immunoprecipitation in a multicenter cohort of patients with IIM [11]. The overall specificity of the line blot is 100 % for anti-Jo1, anti-PL-7, anti-PL-12, and anti-PM/SCL. The commercial line blot has a sensitivity for non-Jo1 antibodies of 4 % and a specificity of 99 % in the diagnosis of IIM, whereas immunoprecipitation has a sensitivity of 11 % and a specificity of 97 % in the diagnosis of IIM. Concordance rate between the line blot and RNA immunoprecipitation is 91 % [11].

High-resolution chest tomography evaluation

HRCT was performed at baseline evaluation with a 1.0- or 1.5-mm-thick axial section taken at 1-cm intervals throughout the entire thorax and was reconstructed using a high spatial frequency algorithm. Between 20 and 25 CT scan images were acquired for each patient. HRCT scans were evaluated by two experts blinded to clinical data (Mejia M and Mateos-Toledo H). Both readers evaluated the HRCTs in an independent way and classified the HRCT images into two groups: (1) ground glass with consolidation images, with or without reticulation, and (2) ground glass and reticulation images without consolidation. All discrepancies were solved by consensus. The fibrotic component, defined by reticular opacities and inflammation by ground glass opacities, was graded according to the Kazerooni [12] and the Goh scores [13]. To evaluate the validity of this evaluation, the reliability between our two experts was evaluated using the intraclass correlation coefficient (ICC). In the case of the Kazerooni score, the ICC between our two readers for fibrosis was 0.75 (95 % confidence interval (CI) 0.53–0.87), and the ICC for ground glass opacities for the Kazerooni score was 0.72 (95 % CI 0.46–0.85). For the Goh score, the ICC was 0.73 (95 % CI 0.49–0.81) in the case of fibrosis. For ground glass opacities, the ICC was 0.90 (95 % CI 0.82–0.95). The scoring of one evaluator (Mejia M) was used for further analysis in the comparison of patients who died and those who survived when using the Kazerooni score. The evaluations done by Mateos-Toledo H were used for the comparison of patients who died and those who survived when the Goh score was used.

Statistical analysis

First, a comparison between patients who died and those who survived was carried out according to the distribution of the

analyzed variable: the χ^2 test, Fisher exact test, rank sum test, or *t* test were done as appropriate. The survival function was estimated with the Kaplan–Meier method. The differences in the survival function in the evaluated groups were compared with the log rank test. A univariate Cox regression analysis was done to estimate the hazard ratio (HR) and its 95 % confidence interval (95 % CI) of the independent variables evaluated, in order to assess its association to time to death (dependent variable). Because of the small sample, multivariable analysis including only two independent variables was carried out. Analyses are two-sided; alpha was set at 5 %. Stata (V 10.1) was used in all analysis.

Results

Forty-three from a total of 45 patients with ARS autoantibodies were included. Of the excluded patients, one was Jo1-positive and the other PL7-positive. Both of them did not have clinical symptoms related to ASS apart from ILD. Most patients were female (34 (79 %)); median age was 47 years old (interquartile range (IQR) 40–56 years old). The majority of patients were Jo1-positive (35 (81.4 %)) and had a median time to diagnosis from the onset of symptoms of 3 months (IQR 1–9 months). Six patients died (14 %). Causes of death were infectious diseases in two patients, myocardial infarction in two patients, progressive respiratory disease with respiratory failure in one patient, and a hemorrhagic stroke in one patient. Of the patients who died, two did so early on after having been received in our institution, within the first month of follow-up. All patients received corticosteroids in variable doses, as well as cyclophosphamide, azathioprine, methotrexate, and leflunomide and the combination of methotrexate and leflunomide. Two patients also received treatment with rituximab with methotrexate, one being Jo1-positive, the other PL7-positive. Both of them had complete remission of the inflammatory myopathy and had an improvement in their ILD. The full description of the cohort may be found in Table 1.

Table 1 Patients included in the study

Variable	*N*=43
Age (years old)[a]	47 (40–57)
Female sex	34 (79 %)
Time between onset of symptoms and diagnosis (months)[a]	3 (1–9)
Jo1-positive patients	35 (81.4 %)
Ej-positive patients	6 (24 %)
PL7-positive patients	2(8 %)
P12-positive patients	0(0 %)
Oj-positive patients	0 (0)
Ro52-positive patients	17/25 (68 %)
Creatin kinase serum levels at baseline (U/l)[a]	624 (256–1529)
Arthritis	30/38 (79 %)
Fever	35 (81 %)
Mechanic's hand sign	25/37 (68 %)
Dermatomyositis rash	6 (14 %)
Proximal muscle weakness	33/41 (80.4 %)
Proximal dysphagia	2 (4.6 %)
Sclerodactyly/scleroderma	5 (11 %)
Raynaud´s phenomenon	9 (21 %)
Interstitial lung disease	43 (100 %)
PaO_2 (mmHg)[a]	57 (46–71.1)
$PaCO_2$ (mmHg)[a]	32 (28.1–36.1)
FVC (% of expected)	69.3±29.13
DLCO, (% of expected)	47 (31–76)
DLCO (ml/min/mmHg)[a]	8.93 (5.88–15.2)
Ground glass and consolidation with or without reticulation (organized pneumonia like pattern)	25 (58 %)
Ground glass, reticulation without consolidation (nonspecific interstitial pneumonia like pattern)	18 (42 %)

[a] Median (IQR)

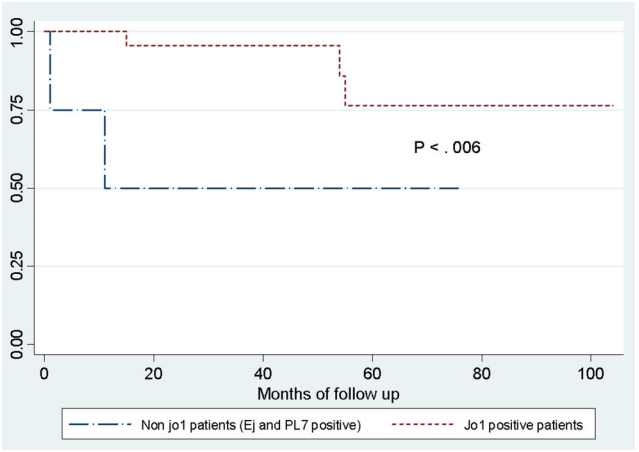

Fig. 1 Kaplan–Meier survival estimates of non-Jo1 patients compared to Jo1 positive patients. Jo1-positive patients had a better prognosis than non-Jo1 patients; log rank test, *P*<.006

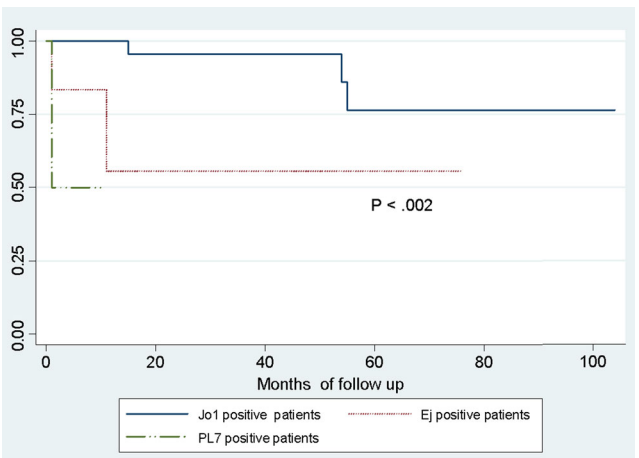

Fig. 2 Kaplan–Meier survival estimates of Jo1-positive patients, Ej-positive patients, and PL7-positive patients. Jo1 patients had better survival than both Ej-positive patients and PL7 patients; log rank test, *P*<.002

Survival analysis

The survival function at 5 years of follow-up was 0.72 (95 % CI 0.43–0.88). Patients who died were different in comparison with survivors in the frequency of anti-Jo1 positivity: Survivors had anti-Jo1 autoantibodies more frequently (86 %) than patients who died (50 %). Figure 1 displays the survival functions of Jo1-positive patients and non-Jo1 patients. The comparison of these survival functions was statistically significant (log rank test P=0.006). Figure 2 displays the survival function of patients according to the three autoantibodies identified in this ASS cohort: Again, there is a difference in the survival function of Jo1-positive patients compared to PL7- and Ej-positive patients (P=0.002). The univariate Cox regression analysis identified five variables associated with survival: Jo1 status, arthritis, extent of ground glass with or without consolidation (inflammation) in HRCT, forced vital capacity at baseline, and the incapacity to do DLCO because of the severity of ILD, with the last variable being strongly associated with FVC <1 l. No difference was found with respect to

Table 2 Comparison between patients who died and survivors

Variable	Patients who died n=6 (14 %)	Patients who survived n=37 (86 %)	HR (95 % CI) P
Age at diagnosis	55 (55–60)	45.5 (39.5–56.5)	1.07 (0.97–1.17) 0.14
Female sex	4 (67 %)	30 (81 %)	0.55 (0.10–3.02) 0.49
Time (months) between onset of symptoms and diagnosis[a]	2(.5–7.5)	3.5 (1–9)	0.93 (0.79–1.11) 0.45
Jo1 positivity	3 (50 %)	32 (86 %)	0.14 (0 .03–.70) 0.02
Creatine kinase serum levels at baseline (U/l)[a]	593.5 (352–1603)	624 (256–1405)	0.9998 (0.9993–1.0002) 0.64
Proximal muscle weakness	5 (83 %)	28/35 (80 %)	1.22 (0.14–10.48) 0.85
Arthritis	3(50 %)	27/32 (84 %)	0.04 (0.003 -.41) 0.007
Proximal dysphagia[b]	0 (0 %)	2 (5.41 %)	P=1.00
Dermatomyositis rash[b]	0 (0 %)	6 (16.2 %)	P=0.57
Ro52 positivity	2/3 (67 %)	15/22 (68 %)	0.86 (0 .07–9.58) 0 .9
Fever at baseline evaluation	5 (83 %)	30 (81 %)	0.71(0.08 - 6.22) 0.76
Goh fibrosis score[a]	3.4 (.93–5)	2.8 (0–4.48)	1.06 (0.92–1.23) 0 .38
Goh inflammation score[a]	43.2 (35.28–54.12)	60.39 (44.64–65.7)	1.06 (1.01–1.11) .02
Kazerooni ground glass score[a]	3.08 (2.66–3.5)	2.5 (2.3–2.66)	5.87 (1.43–24.01) 0.02
Kazerooni fibrosis score[a]	.415 (.33–1.3)	0 (0–.83)	2.43 (0 .59–9.9) 0.21
Forced vital capacity (% of expected)[a]	33 (28–56)	59 (42–75)	0.93 (0.88–0.99) 0 .04
DLCO (% of expected)[c]	47 (30–78)	48.5 (31–66)	.95 (0.89–1.02) 0.24
Patients unable to do DLCO because of severity of ILD	4 (67 %)	6 (16 %)	7.31 (1.33–40) 0.03

[a] Median (IQR)

[b] Exact Fisher test. The lack of patients with dysphagia in patients who died did not allow an estimation of HR

[c] Data of 33 patients; DLCO could not be done in patients with severe pulmonary disease or with FVC <1 l

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medical treatment used. “”Table 2 shows the results of the univariate Cox regression analysis with the estimated HR and 95 % CI. In order to assess for confounding, two multivariable Cox regression models were elaborated with survival as the dependent variable; in the first one, including Jo1-positive and Goh inflammation score, the adjusted HRs were 0.004 (95 % CI 0.00003–0.54, P=0.03) and 1.08 (95 % CI 1.003–1.17, P=0.042) respectively, whereas in the second model including as independent variables Jo1-positive and Kazerooni ground glass score, the corresponding HRs were 0.0037 (95 % CI 0.00003–0.38, P=0.018) and 7.68 (95 % CI 1.37–43.03, P=0.02). A third multivariable model was elaborated in order to adjust for Jo1 positivity with time between symptom onset until diagnosis; the HRs were 0.00043 (95 % CI 0.00002–0.88, P=0.045) and 0.76 (95 % CI 0.56–1.02, P=0.08)

Comparison between Jo1-positive patients with non-Jo1 (Ej- or PL7-positive) patients

There was a statistical tendency toward a difference in the time between the onset of symptoms and diagnosis: non-Jo1-negative patients tended to have a delayed diagnosis compared to Jo1-positive patients (P=0.08). Jo1-positive patients had arthritis more frequently than non-Jo1 patients (P=0.05). Besides that, there were no differences in clinical manifestations and extension of lung disease (Table 3).

Discussion

In this study, designed to evaluate factors associated with mortality in patients with the ASS and ILD, the results show that the serological status of patients (Jo1-positive vs non-Jo1), the extent of lung inflammation in the HRCT scan, a low baseline vital forced capacity, and the presence of arthritis are associated with survival in this group of patients.

As previously reported [6, 14], Jo1 status seems to be associated with prognosis in the ASS. In this work, restricted to ASS patients with ILD, Jo1 patients had better survival rates compared to non-Jo1 patients. Previously, many authors have independently reported that non-Jo1 ASS patients have a higher incidence of ILD during the course of disease and that features associated with survival in ASS are mainly related to pulmonary involvement [4, 14–21]. It seems reasonable therefore that the higher mortality observed in ASS non-Jo1 patients is secondary to a higher prevalence and severity of ILD in non-Jo1 patients. In this regard, our results seem relevant because all included patients had ILD, so the possibility of a higher mortality in non-Jo1 patients because of a higher prevalence of ILD can be ruled out. We evaluated the extension of lung inflammation and fibrosis using two indexes: the Goh score and the Kazerooni index. Both methods were consistent with the fact that the extension of lung inflammation is associated with mortality in ASS. We also elaborated two multivariable models in which the extension of inflammation was evaluated and adjusted for the presence of Jo1 autoantibodies.

Table 3 Comparison between Jo1 positive patients and non-Jo1 (Ej or PL7 positive) patients

Variable	Jo1-positive n=35	Non-Jo1 n=8	P
Age at diagnosis of ASS[a]	45 (39–55)	58 (46–61)	0.11
Female sex	27 (79 %)	7 (87.5 %)	1.0
Time between onset of symptoms and diagnosis[a]	2 (1–5)	5 (4–12)	0.08
Creatine kinase serum levels at baseline (U/l)[a]	649 (256–2095)	467 (287.5–653)	0.36
Proximal muscle weakness[a]	28/33 (85 %)	5/8 (62 %)	0.17
Mechanic’s hand sign	19/29 (65 %)	6 (75 %)	1.0
Ro52 positivity	10/17 (59 %)	7/8 (87.5 %)	0 .20
Arthritis	26/30 (87 %)	4 (50 %)	0.05
Fever at baseline evaluation	29/35 (83 %)	6/8 (75 %)	0.63
Goh fibrosis score[a]	2.72 (0–5.75)	3.92 (2.61-5)	0 .37
Goh inflammation score[a]	41.68 (34 -52.71)	44.2 (28–51.52)	0.77
Kazerooni fibrosis score[a]	0 (0–.74)	.5 (.33–1.16)	0 .10
Kazerooni ground glass score[a]	2.55 (2.33–3)	2.33 (2–2.6)	0 .20
Forced vital capacity (% of expected)[a]	59 (39.5-78)	57.5 (38.5–64.5)	0 .50
DLCO (% of expected)[b]	47 (30.5–79)	34 (32–54)	0.46
Patients unable to do DLCO because of severity of ILD	7 (20 %)	3 (37.5 %)	0.32

[a] Median (IQR)

[b] Data of 33 patients; DLCO could not be done in patients with severe pulmonary disease or with FVC <1 l

Both models showed that Jo1 positivity and the extension of lung inflammation are independently associated with mortality.

Another proposed explanation of the higher mortality observed in non-Jo1 patients may be a delayed diagnosis compared to Jo1-positive patients. We also explored this possibility in our study. Our results did not show any differences in the time to diagnosis of ASS in patients who survived and those who passed away, although non-Jo1 ASS had a tendency toward a delayed diagnosis (P=0.08). A third multivariable model was elaborated in order to adjust for the Jo1 and delayed diagnosis with its association with survival. In this case, no confounding effect was found and the adjusted HRs for Jo1 and time from symptoms onset until diagnosis were basically unchanged.

The results of our study should be interpreted in the context of an ILD clinic and may have no validity outside an ILD clinic. Nevertheless, the results of this study may have clinical relevance: non-Jo1 patients with ASS may benefit from more aggressive treatments early on after medical diagnosis. Also, the results of our study give a high priority of obtaining the non-Jo1 ARS autoantibodies of patients with symptoms suggesting ASS and ILD, and finally, in the planning of clinical trials, randomization must be done according to this possible confounder: Randomization blocks must be done according to the ARS autoantibody.

The commercial diagnostic line blot used in this study allows clinicians treating ILD patients to screen individual patients for the occurrence of rare autoantibodies. Although the line blot may have less sensitivity when evaluating anti-ARS non-Jo1 autoantibodies compared to RNA immunoprecipitation (4 vs 11 %), it has very good specificity when compared to RNA immunoprecipitation (99 vs 97 %) [11]. Moreover, the prognostic relevance of the non-Jo1 positivity status regarding survival, detected by the line blot, points strongly to the clinical relevance of using this line blot assay that is more feasible to clinicians than RNA immunoprecipitation.

There were other variables associated with survival: Patients who survived had arthritis more frequently than those who died. One possible explanation is that patients who died were more often evaluated for the first time by a rheumatologist after being treated with fluids and being on mechanical ventilation, making the clinical evaluation of arthritis more difficult. Another explanation is that non-Jo1 patients have less prevalence of arthritis and the association of arthritis and survival is confounded by non-Jo1 autoantibodies. Other variables associated with survival were low forced vital capacity at baseline and no capacity to do a DLCO. Both variables are related to each other and to the extension of lung inflammation in the HRCT scan. Our data did not allow us to evaluate differences in the prognosis according to medical treatment.

In the comparison between Jo1-positive patients and non-Jo1 patients, Jo1-positive patients had arthritis more frequently than non-Jo1 patients as has been previously described by other authors [6, 17]. We did not find any other difference between Jo1-positive patients and non-Jo1 patients.

Our study has several limitations; one is the small sample size, which limits the conclusions of the multivariable analysis, meaning that the results of the multivariable analysis must be interpreted with caution. Nevertheless, ASS is a rare and severe disease so a single-center study is relevant in this scenario. Another limitation is that the Goh and the Kazerooni scores were designed to evaluate ILD in systemic sclerosis and idiopathic pulmonary fibrosis, respectively. Nevertheless, both indexes have been used to evaluate ILD in other conditions including ILD in inflammatory myopathies [22] and interstitial lung disease related to rheumatoid arthritis [23–25] with apparent good performance. Another limitation is that non-Jo1 patients were only PL7 and Ej patients; we did not find any Oj-positive or PL12-positive patients. Furthermore, there are other anti-ARS antibodies that we did not measure: anti-SC, anti-KS, anti-JS, anti Ha, anti-tryptophanyl, and anti Zo. And, finally, our results may have validity only in the clinical scenario of patients with ASS and ILD.

In conclusion, our study confirms the previous observation that non-Jo1 patients have worse survival rates than Jo1 patients. Other factors associated with survival include the extension of lung involvement, a low forced vital capacity at baseline evaluation, and the presence of arthritis. The results of this study support the concept that a thorough evaluation of ASR autoantibodies in patients with ASS may be very important in the clinical evaluation of this group of patients and may be relevant in the planning of clinical trials.

Disclosures None.

Founding source There is no founding source for this study.

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